WNK kinases, including WNK3, and the associated downstream Ste20/SPS1-related proline-alanine-rich protein kinase (SPAK) and oxidative stress responsive 1 (OSR1) kinases, comprise an important signaling cascade that regulates the cation-chloride cotransporters. Ischemia-induced stimulation of the bumetanide-sensitive Na(+)-K(+)-Cl(-) cotransporter (NKCC1) plays an important role in the pathophysiology of experimental stroke, but the mechanism of its regulation in this context is unknown.

With-no-lysine kinase (WNK) and Na+-K+-2Cl- cotransporter 1 (NKCC1) are involved in the pathogenesis of hypertension.

In a study Bhuiyan et al., investigated, the WNK-NKCC1 signaling pathway in spontaneously hypertensive rats (SHR) and their associated susceptibility to stroke injury. Basal NKCC1 protein levels were higher in SHR than in normotensive Wistar Kyoto (WKY) rat brains. After inducing ischemic stroke, adult male WKY and SHR received either saline or NKCC1 inhibitor bumetanide (10 mg/kg/day, i.p.) starting at 3-h post-reperfusion. NKCC1 inhibition blunted the extent of ischemic infarction in SHR and improved their neurobehavioral functions. Interestingly, ischemia led to increased NKCC1 phosphorylation in SHR but not in WKY rats. Pronounced elevation of WNK1, WNK2 and WNK4 protein and downregulation of WNK3 were detected in ischemic SHR, but not in ischemic WKY rats. Upregulation of WNK-NKCC1 complex in ischemic SHR brain was associated with increased Ca2+-binding protein 39 (Cab39), without increases in Ste20-related proline alanine-rich kinase or oxidative stress-responsive kinase-1. Moreover, subacute middle cerebral artery stroke human brain autopsy exhibited increased expression of NKCC1 protein.

They conclude that augmented WNK-Cab39-NKCC1 signaling in SHR is associated with an increased susceptibility to ischemic brain damage and may serve as a novel target for anti-hypertensive and anti-ischemic stroke therapy [1)]

1)
Bhuiyan MI, Song S, Yuan H, Begum G, Kofler J, Kahle KT, Yang SS, Lin SH, Alper SL, Subramanya AR, Sun D. WNK-Cab39-NKCC1 signaling increases the susceptibility to ischemic brain damage in hypertensive rats. J Cereb Blood Flow Metab. 2016 Oct 26. pii: 0271678×16675368. [Epub ahead of print] PubMed PMID: 27798271.